

UBB+1, an important switch in the onset of Alzheimer's disease

Citation for published version (APA):

Gentier, R. G. J. (2015). UBB+1, an important switch in the onset of Alzheimer's disease. [Doctoral Thesis, Maastricht University]. Uitgeverij BOXPress. <https://doi.org/10.26481/dis.20151105rg>

Document status and date:

Published: 01/01/2015

DOI:

[10.26481/dis.20151105rg](https://doi.org/10.26481/dis.20151105rg)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

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Valorization

Societal relevance

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia accounting for 60-80% of all dementia patients (Barnes and Yaffe, 2011). It is a very complex disease because of its multifactorial nature and it is characterized by a decline in cognition, language, planning and solving skills, as well as behavioral changes affecting a person's everyday activities. AD patients in the final stage of the disease are bedridden and the disease is ultimately fatal. Currently, there are over 5 million Americans suffering from AD while in The Netherlands, around 140.000 people are currently suffering from this disease. These numbers are expected to triple around 2050. AD is the 6th leading cause of death and it kills more people than breast and prostate cancer combined. It is a devastating disease which cannot be slowed, stopped or prevented. Between 2000 and 2013 deaths of other diseases (including heart disease, stroke, breast and prostate cancer, and HIV/AIDS) decreased, while AD deaths increased 71% in the USA. It causes an enormous economic burden, and in 2015 the disease will cost the US nation \$226 billion and an amount that is estimated to increase to \$1.1 trillion by 2050. By 2030, 72 million baby boomers will reach the age to be at greater risk for developing AD. Less than 50% of people with AD are being told of their diagnosis (Alzheimer's Association 2015). These data together illustrate the impact of this tragic disease on society. Researchers have a pivotal task to make early detection possible, to find a way to slow down the disease progression, and to unravel the cause(s) and the molecular mechanisms behind it to come with a drug or a therapy to prevent and/or reverse the disease. The goal of the present thesis was to help unraveling the molecular mechanisms behind the disease.

Diagnosis of AD

Diagnosing AD is difficult as no simple test is available and is most commonly made by a general practitioner. A wide variety of tools and lists are present to diagnose the disease. Making the diagnosis is usually based on the medical anamnesis and family history, information from a person of the intimate circle of the patient, cognitive tests, DSM-V criteria and neurological examinations and MRI (Alzheimer's Association 2015). A definite diagnosis of AD is only possible postmortem after macro- and microscopic examination

of the brain based on brain atrophy and the presence of extracellular plaques and neurofibrillary tangles in the brain. Researchers believe that early detection will be key to preventing, slowing and stopping AD. Therefore, in the last decade researchers have spent much effort in research on early detection of AD. Research has been performed on the selection of suitable biomarkers for the diagnosis for AD. One of these are the biomarkers showing the level of A β accumulation in the blood or cerebrospinal fluid (CSF). Other research groups are examining the comorbidities of AD:

- a. Olfactory dysfunction is associated with aging, represented by a progressive decline in the ability to detect, identify and discriminate odors (Mobley et al., 2014). Olfactory deficits have been described in AD as well and it is a predictor of the incidence of mild cognitive impairment (MCI) and of the conversion of MCI to AD (Djordjevic et al., 2008;Attems et al., 2014).
- b. Age-related auditory deficits are also quite common in the elderly. It has been shown that structural changes are present in the central auditory pathways of AD patients (Sinha et al., 1993). An increased risk of AD is present in individuals with central auditory dysfunction (CAD) and it is suggested that CAD is an early manifestation of AD that occurs before any sign of cognitive decline. Therefore, auditory dysfunction may be a valuable tool to diagnose AD at an early stage.
- c. An important comorbidity of AD is depression which may precede the clinical symptoms of AD by several years (Sierksma et al., 2010). However, it is unclear whether depression is a risk factor (Geerlings et al., 2008) or a prodromal sign (Wilson et al., 2004) for dementia and AD.
- d. The basal ganglia including a network of dopaminergic subunits, are essential in the reward and reinforcement mechanisms and in regulating emotional behaviour (de Jong et al., 2011), as well as motor functions. Feelings of apathy have been noted in AD patients which correlated with the detection of dopaminergic dysfunction. Apathy was ascribed in 47% of patients with mild AD and increased event to 80% in patients with severe AD (Mitchell et al., 2011).
- e. Respiratory problems and swallowing impairments are common in AD patients and frequently result in aspiration pneumonia. It is suggested that changes in cortical control of swallowing may begin long before dysphagia becomes apparent

(Humbert et al., 2010). These basic functions are regulated by the nucleus of the solitary tract (NTS) and the parabrachial nucleus (PBN) in the brainstem. The present thesis showed changes in spontaneous breathing patterns and altered hypoxic response in UBB⁺¹ tg mice (an AD mouse model), suggesting a central dysfunction of respiratory regulation.

It would be worthwhile to take possible comorbidities of AD into account in order to come earlier to a more accurate diagnosis of AD as some are present long before any sign of cognitive dysfunction. The present thesis demonstrated the accumulation of UBB⁺¹ in an AD tg mouse model (line 3413), pointing to the involvement of a dysfunctional UPS in AD. For some anatomical regions (NTS, PBN, raphe nuclei and nucleus basalis of Meynert (NBM)) we showed UBB⁺¹ accumulation in the same regions in the human brain compared with the mouse brain. Besides this, we also examined the accumulation of plaques and tangles in olfactory bulb (OB), inferior colliculus (IC), basal ganglia and raphe nuclei and the respiratory brain stem areas. We confirmed earlier studies and showed the presence of these hallmarks of pathology in the different anatomical regions.

As AD is a multifactorial disease, researchers have to take every possible causative factor into account to come to a therapy or an early diagnosis of this disease. The present thesis expanded knowledge about UBB⁺¹ accumulation in the tg mouse brain as well as in the human brain. We emphasized the role of UBB⁺¹ in different comorbidities of AD and concluded that comorbidities can be very pivotal to come to an early diagnosis of this neurodegenerative disease. The earlier the diagnosis of AD the lower the health care costs and the higher the quality of life are for the patient and family.

Possible therapeutic applications

Currently, no effective pharmacological drug or therapy is available to prevent, stop or cure AD because of the complexity of the disease. Future perspectives are dramatic as the total number of patients will increase enormously and a solution for this neurodegenerative disease is necessary. It is a race against time for researchers to come with a therapy. Several treatment options are used today in the clinic today like cholinesterase inhibitors. These inhibitors prevent the breakdown of the neurotransmitter acetylcholine which is pivotal for learning and memory. Unfortunately, it only delays worsening of symptoms for 6 to 12 months on average for around 50% of patients taking these inhibitors. An NMDA receptor antagonist which regulates the activity of another neurotransmitter involved in learning and memory called glutamate is currently also given to AD patient. It retards the progression of the symptoms temporarily for some AD patients. In addition to date, immunization trials in AD patients have not been effective in terms of ameliorating or curing dementia. Probably these trials started too late in the disease progression (Lannfelt et al., 2014). Removal of A β in AD brains has been questioned because studies show that the amount and distribution of A β accumulation do not correlate with the degree of cognitive impairment and in addition A β is present as well in the brains of cognitively normal elderly people (Drachman, 2014). It has been shown that immunisation with A β ₄₂ resulted in clearance of amyloid plaques in patients with AD but this clearance did not prevent progressive neurodegeneration (Holmes et al., 2008). The use of γ -secretase inhibitors were unsuccessful as well so far, as the clinical trials were disappointing, possibly due to lack of knowledge of their working mechanism (De Strooper, 2014).

After several failures in developing AD therapies, other aspects, which potentially contribute to AD progression, come into focus for the development of therapeutics. Recent data suggest that a dysfunctional UPS is an early and causative event for AD progression, and a prime target for AD therapeutics (Manavalan et al., 2013; IGAP, 2015). The present thesis elaborates new insights in the genesis of the disease considering this aspect. Preventing the accumulation of the AD-associated UBB⁺¹, which impairs the UPS at high levels, could be a promising approach for promoting neuronal survival, thereby delaying the progression of AD. Chapter 6 shows that UPS impairment upon UBB⁺¹ accumulation

causes mitochondrial damage. We identified the UBB⁺¹-induced enhancement of the basic amino acids arginine, ornithine and lysine at mitochondria as a toxic event causing damage to the mitochondria. Hereby the protein cytochrome c and other factors can be released which eventually will lead to cell death.

In parallel, we identified a mechanism which protects the cell against the harmful effects of UBB⁺¹. A protein called Vms1 can relieve the UBB⁺¹-triggered mitochondrial dysfunction and cell death. Our study proposed that Vms1-dependent mitochondrial quality control might retard the AD associated neuronal dysfunction. We believe that AD-induced cellular dysfunctions can be avoided by UPS activity at mitochondria has far-reaching pathophysiological implications.

The present thesis (Chapters 5 and 6) also revealed another possibility to develop therapeutic applications. A decrease in A β plaque load in APPPS1/UBB⁺¹ tg mice is caused by rises in γ -secretase activity/PS1 expression. In the current scientific paradigm it is thought that it is necessary to inhibit the γ -secretase activity as PS1 is responsible for the cleavage of APP C-terminal fraction (APP-CTF) and thereby creates A β which will accumulate in A β plaque load. However, as mentioned above, until now treatments with γ -secretase inhibitors were so far unsuccessful (De Strooper, 2014). Therefore, based upon our results in the triple tg APPPS1/UBB⁺¹ line, we suggest to examining the effects of activation of γ -secretase activity. We anticipate finding lower number of A β plaques which possibly will have an effect on behavioural read-outs.

Both ideas mentioned above for possible therapeutic applications are molecular hypotheses which need more input. However, such research is still in its infancy, so both approaches are valuable options to investigate further and hopefully contribute to an amelioration or cure for AD.

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